Practical methods to pool multi-study joint longitudinal and time to event data

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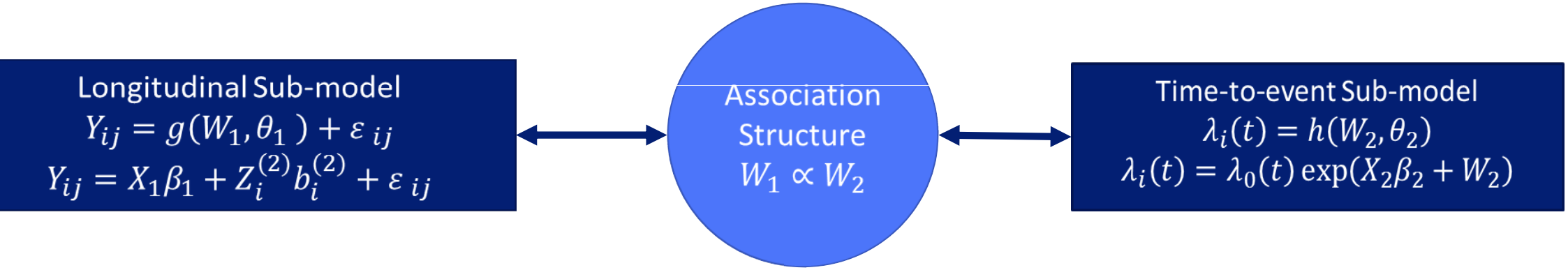
oint longitudinal and time-to-event data (single study)

- Methods to simultaneously model potentially related longitudinal and time-to-event da
- Can produce less biased more efficient results than standalone cases where linked longitudinal and time-to-event data exists

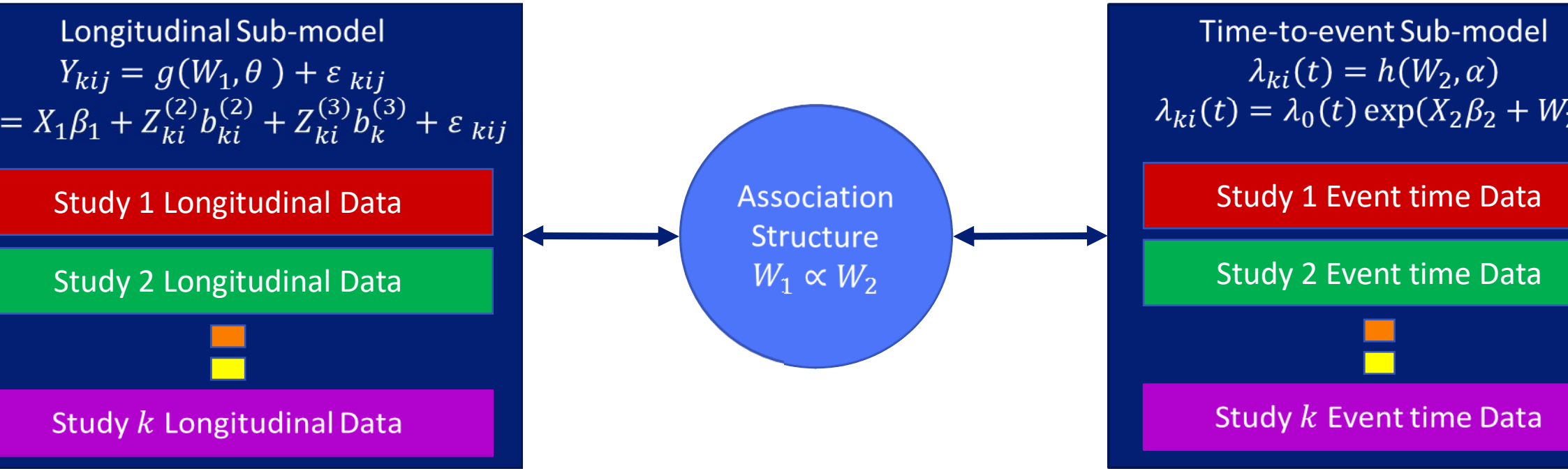


Meta-Analysis (MA)

Systematic pooling of results from multiple studies
Allows increased precision, identification of effect sizes too small to be identified in single studies, and allows questions additional to those originally posed in the data to be answered
Gold standard – Individual Participant/Patient Data (IPD) meta-analyses, where data for each individual recorded in studies identified in the meta-analysis is available.

oint longitudinal and time-to-event data (multi-study)

- Data available from multiple studies
- Clustering of data within studies must be accounted for (e.g. through random effects, interaction terms, stratified baseline hazard)



pproaches to modelling multi-study IPD joint data

Two main approaches – one stage or two stage

Two stage approaches

- Separate joint models fitted to data from each study
- Results from each study pooled using standard meta-analytic techniques

One stage approaches

- Joint model fitted to meta-dataset (containing data from all studies)
- Clustering of data must be accounted for

eal Data – subset of the INDANA dataset

IPD from multiple studies investigating the effect of no treatment versus any treatment for hypertensive patients

Longitudinal data measured at baseline, 6 months, then annually thereafter to maximu of 7 years. Measurement patterns varied between studies

Examining longitudinal outcome systolic blood pressure and time-to-event outcome tim to death

Evidence of a changepoint in the data at 6 month, so $\exp(-3 * time)$ term included in the model

Two stage methods

wo stage methods - overview

1: Joint model fitted to data from each study

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_0(t) \exp(\beta_{21} treat_{ki} + W_2)$$

$$W_2 = \alpha^{(2)}(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki})$$

2: Study specific parameters pooled using standard meta-analytic techniques

verse variance method used (DerSimonian method used for random meta-analyses)
oth fixed and random effects meta-analyses fitted and compared
parate meta-analyses for each parameter of interest

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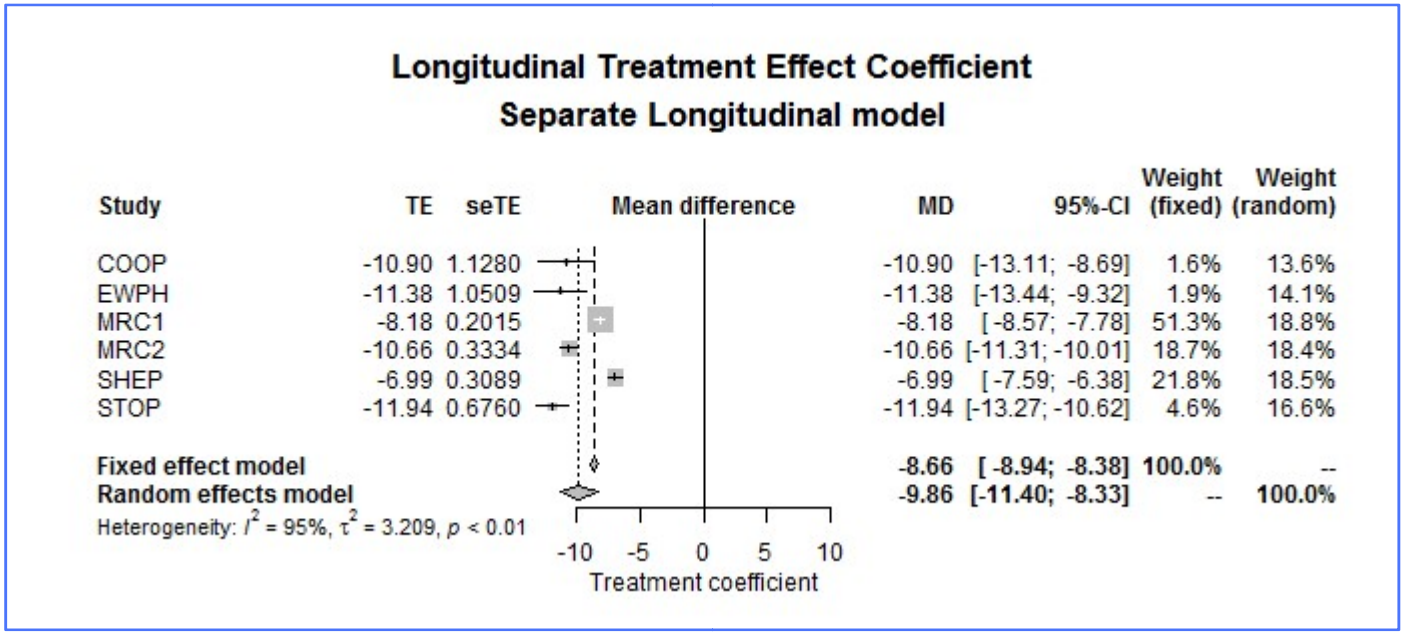

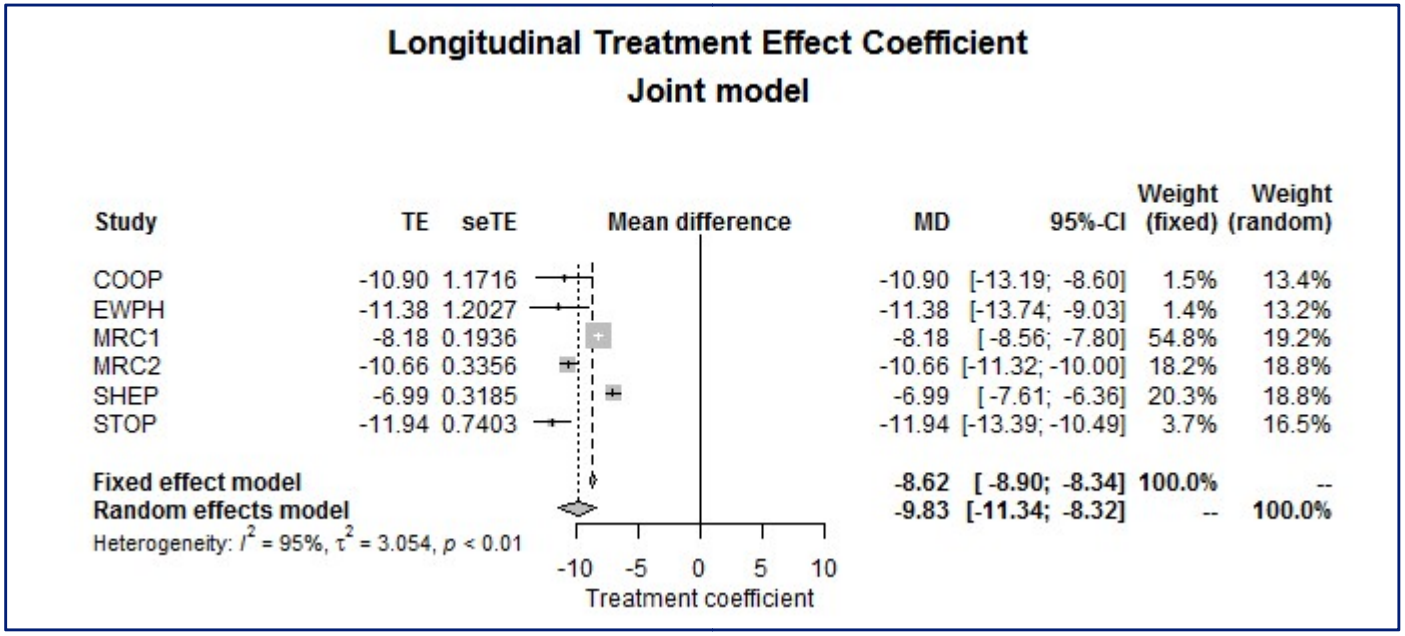

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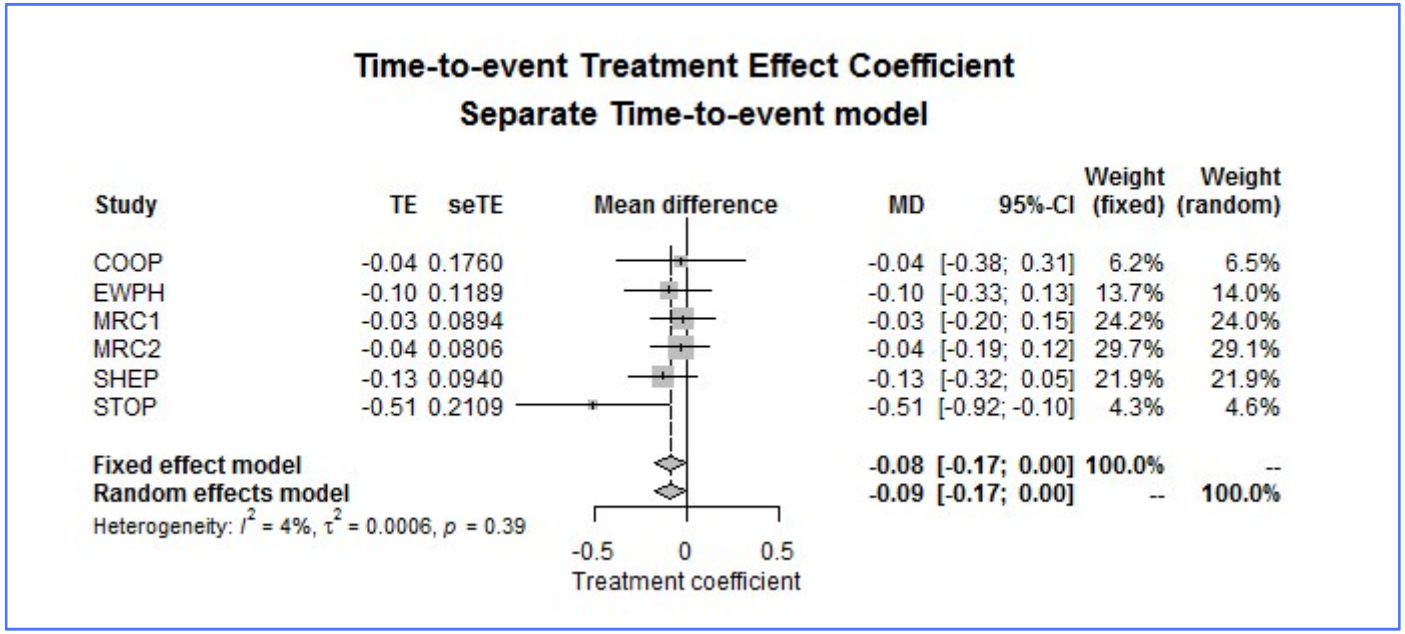

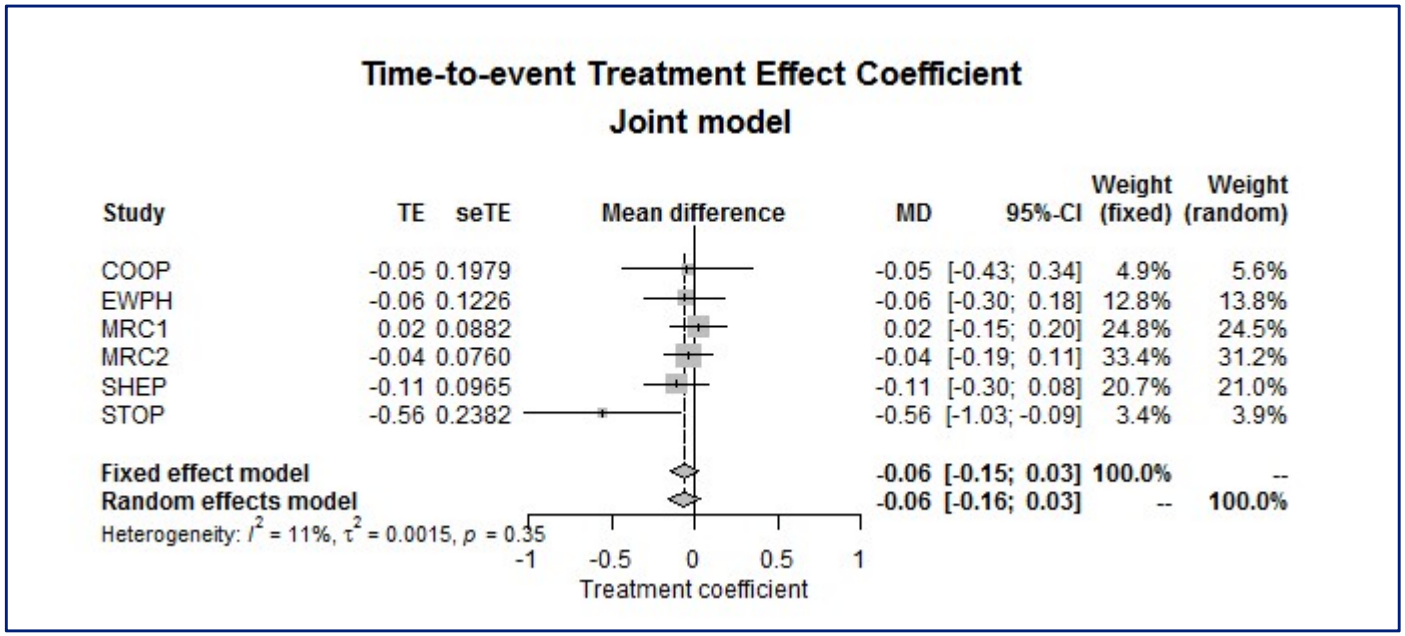

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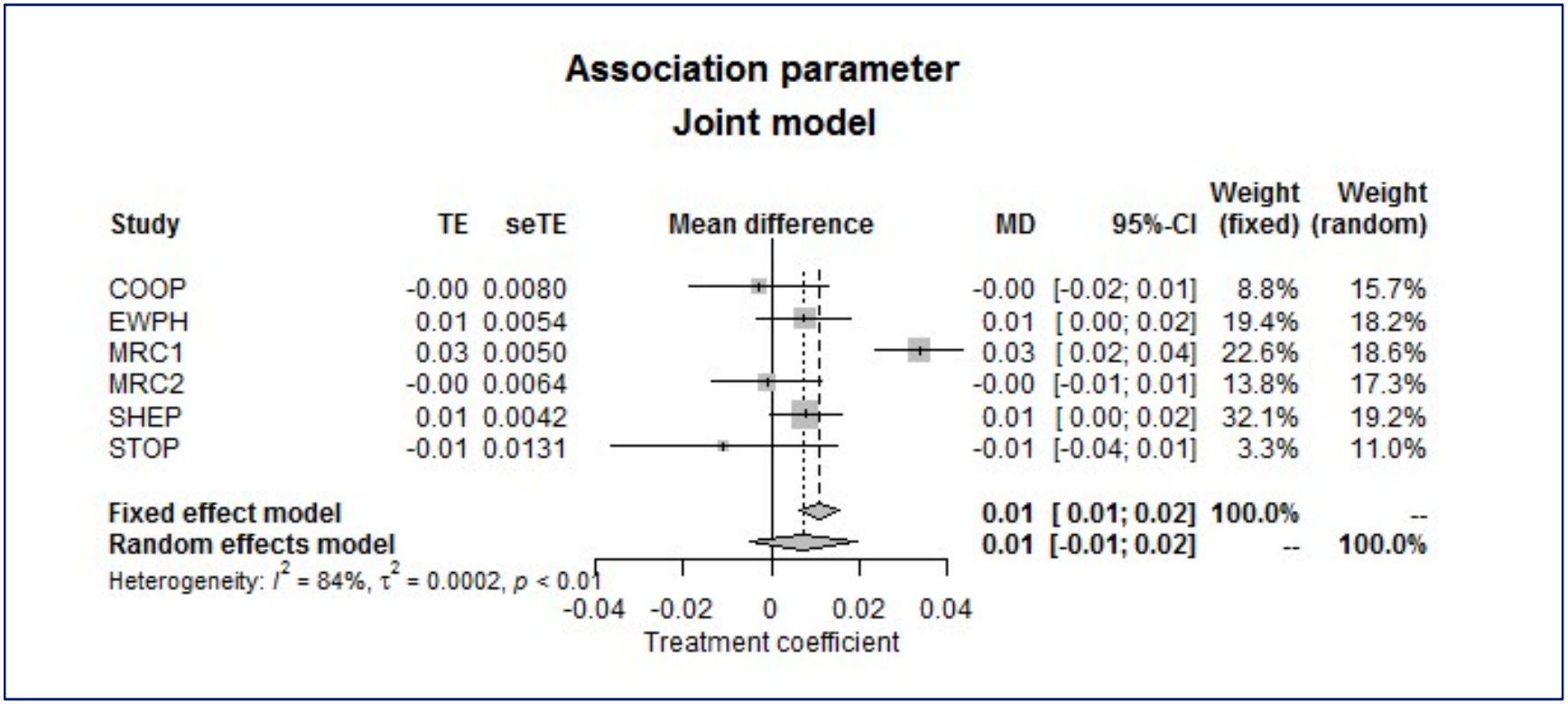

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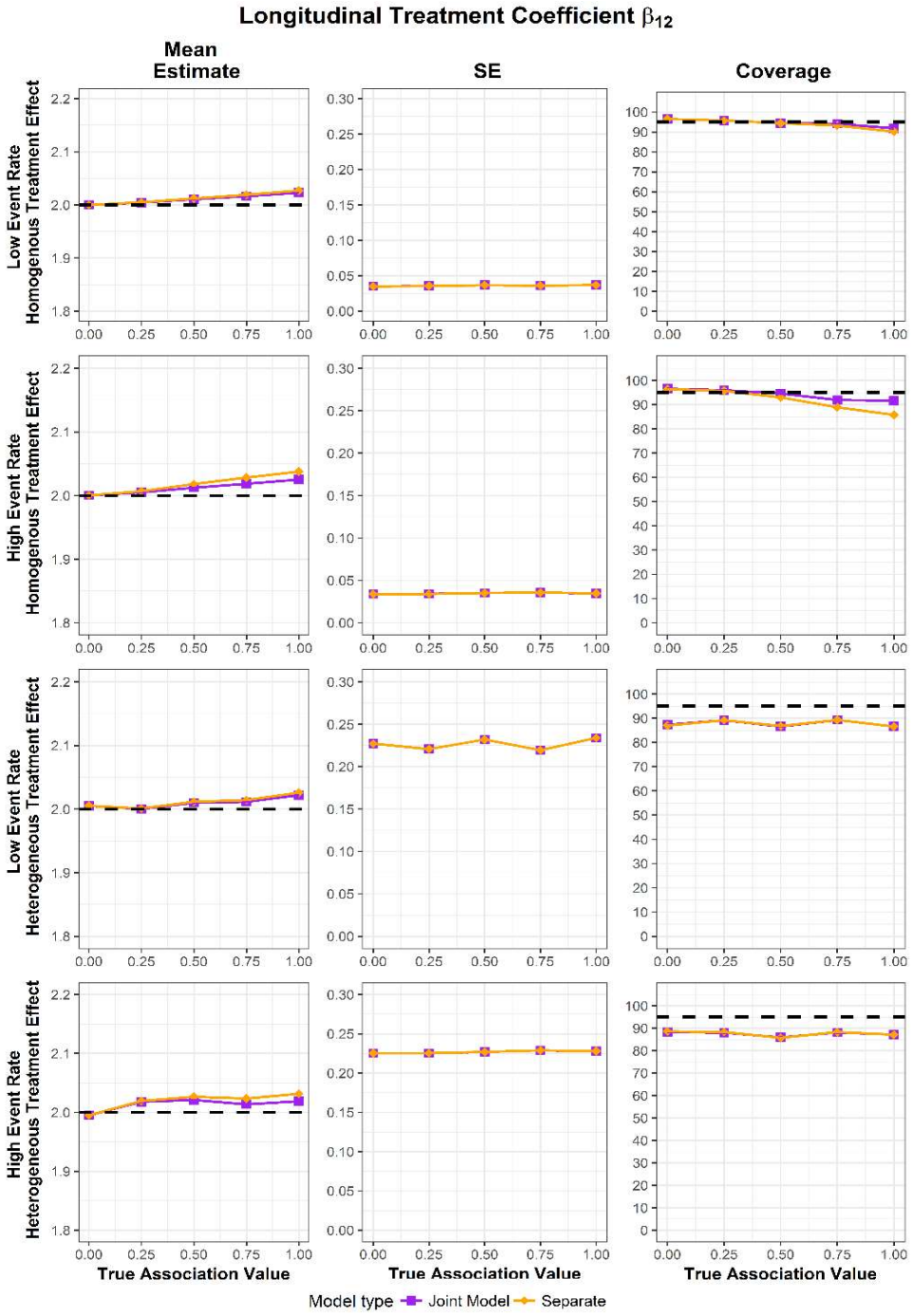

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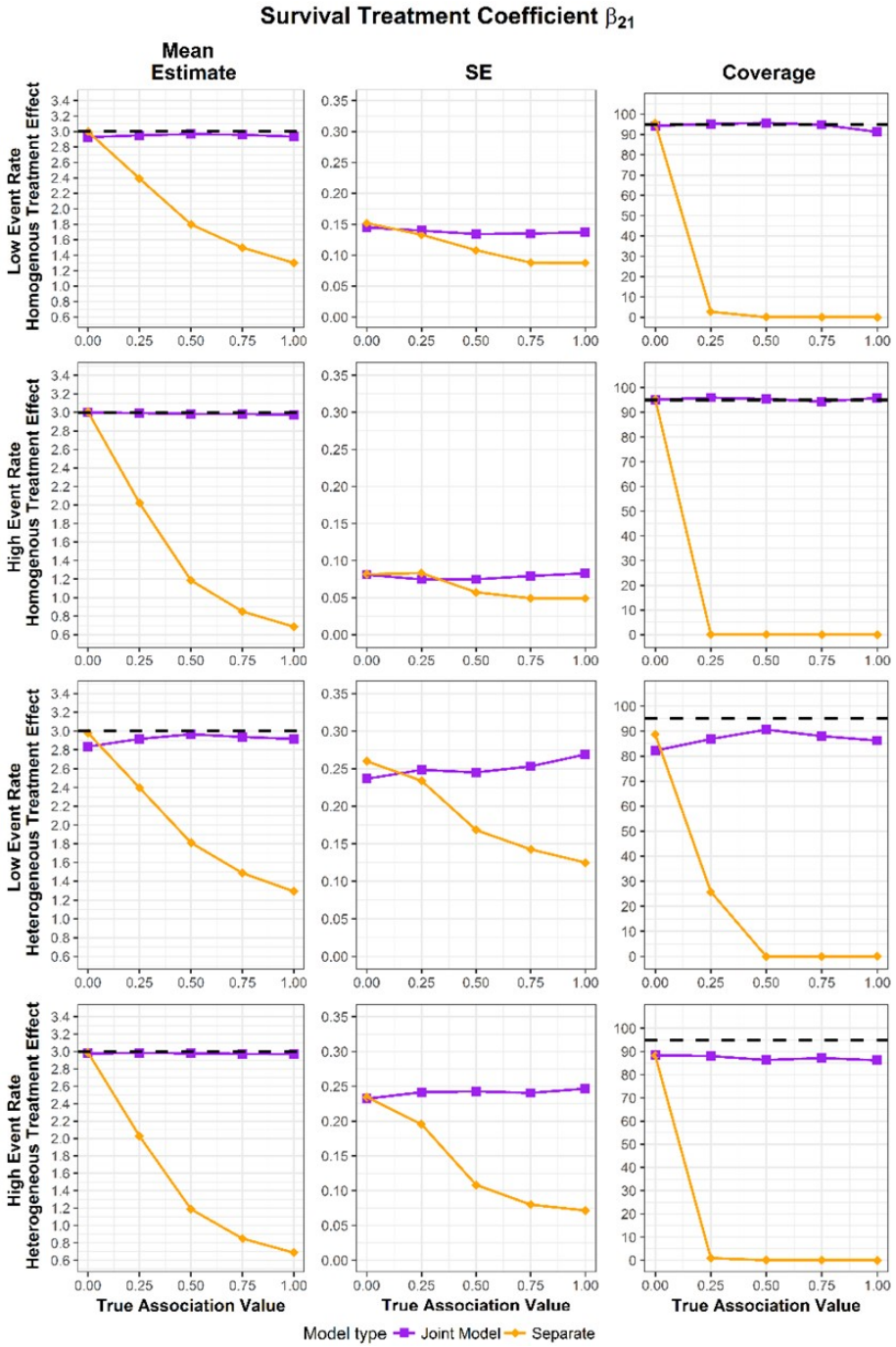


wo stage methods - recommendations

reliminary work

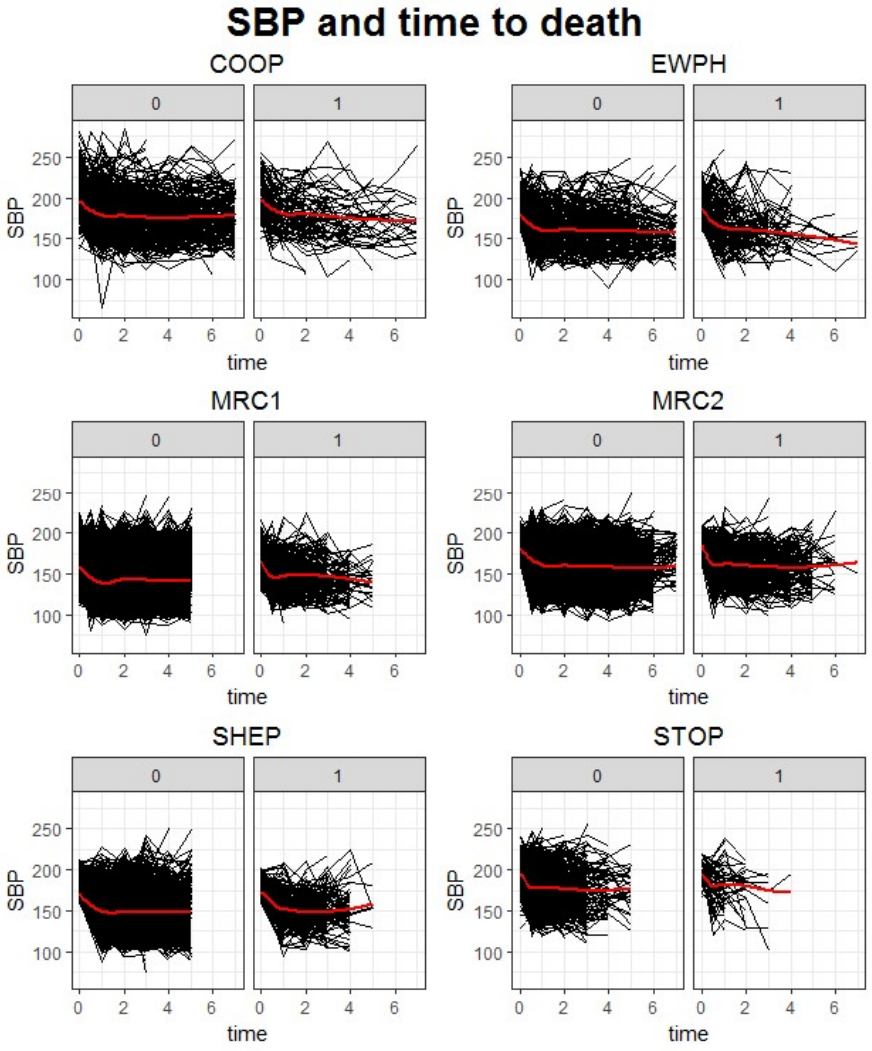
For each study:

- Plot longitudinal trajectories separately for those experiencing an event and those censored.
- Produce Kaplan-Meier plots for e.g. each treatment group

Use plots to assess whether an association between longitudinal and time-to-event outcomes is feasible

Use plots and clinical background of the data to select:

- Longitudinal sub-model
- Time-to-event sub-model
- Association structure



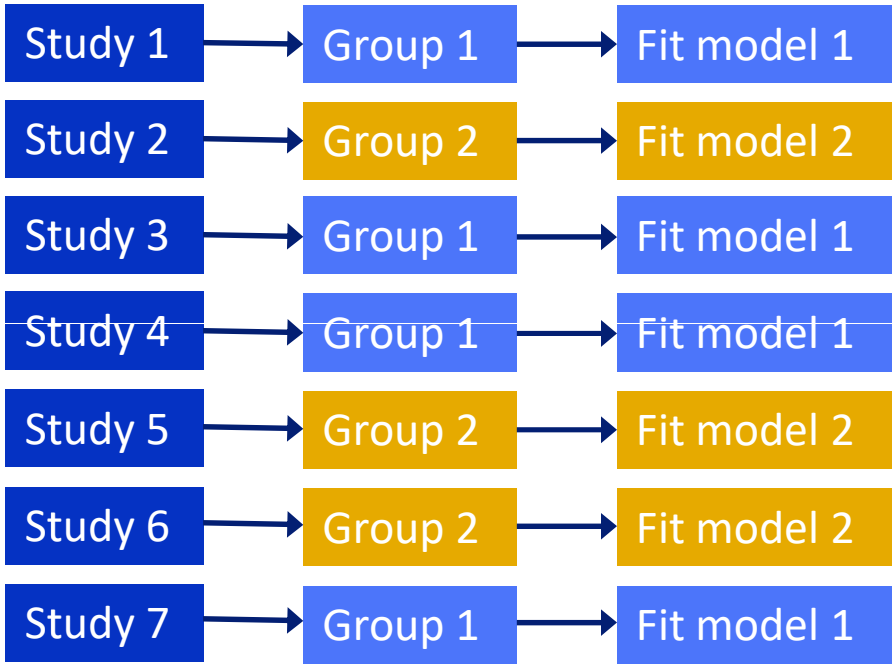
wo stage methods - recommendations

st Stage

Group studies such that chosen model structure within each group is identical.

Within each group, fit identical joint models to data from each study.

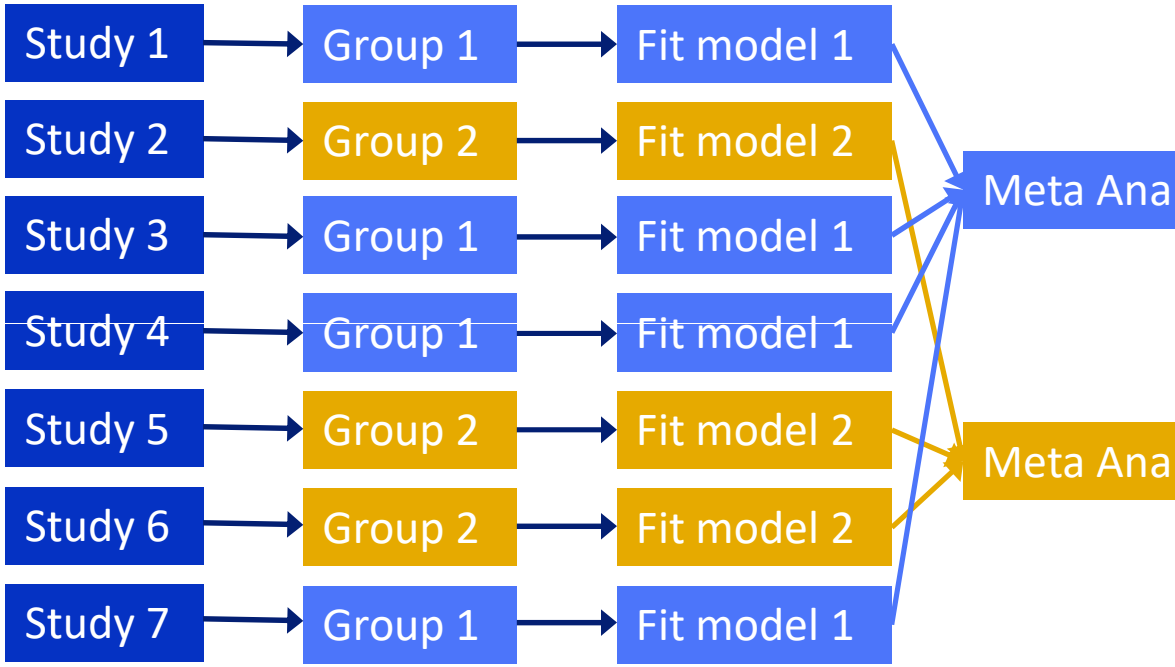
Model structures can differ between groups.



wo stage methods - recommendations

cond Stage

- For each study extract model parameters, precision estimates and sample size
- Pool estimates within groups using standard MA techniques.



One stage methods

ne stage methods– Group 0 – Naïve model

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_0(t) \exp(\beta_{21} treat_{ki} + W_2)$$

$$W_2 = \alpha^{(2)}(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki})$$

ne stage methods - Group 1 – Fixed Interaction terms

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + \beta_{14} study_{ki} + \beta_{15} treat_{ki} * study_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_0(t) \exp(\beta_{21} treat_{ki} + \beta_{22} study_{ki} + \beta_{23} treat_{ki} * study_{ki} + W_2)$$

$$W_2 = \alpha^{(2)}(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki})$$

ne stage methods - Group 2 – Fixed effects and one study level ndom effect

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + \beta_{14} study_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + b_{1k}^{(3)} treat_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_0(t) \exp(\beta_{21} treat_{ki} + \beta_{22} study_{ki} + W_2)$$

$$W_2 = \alpha^{(2)} \left(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} \right) + \alpha^{(3)} \left(b_{1k}^{(3)} treat_{ki} \right)$$

ne stage methods– Group 3 –Study level random effects

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + b_{0k}^{(3)} + b_{1k}^{(3)} treat_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_0(t) \exp(\beta_{21} treat_{ki} + W_2)$$

$$W_2 = \alpha^{(2)} \left(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} \right) + \alpha^{(3)} \left(+ b_{0ki}^{(2)} + b_{1k}^{(3)} treat_{ki} \right)$$

ne stage methods – Group 4 – Fixed effects, stratified baseline haz

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + \beta_{14} study_{ki} + \beta_{15} treat_{ki} * study_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_{0k}(t) \exp(\beta_{21} treat_{ki} + W_2)$$

$$W_2 = \alpha^{(2)}(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki})$$

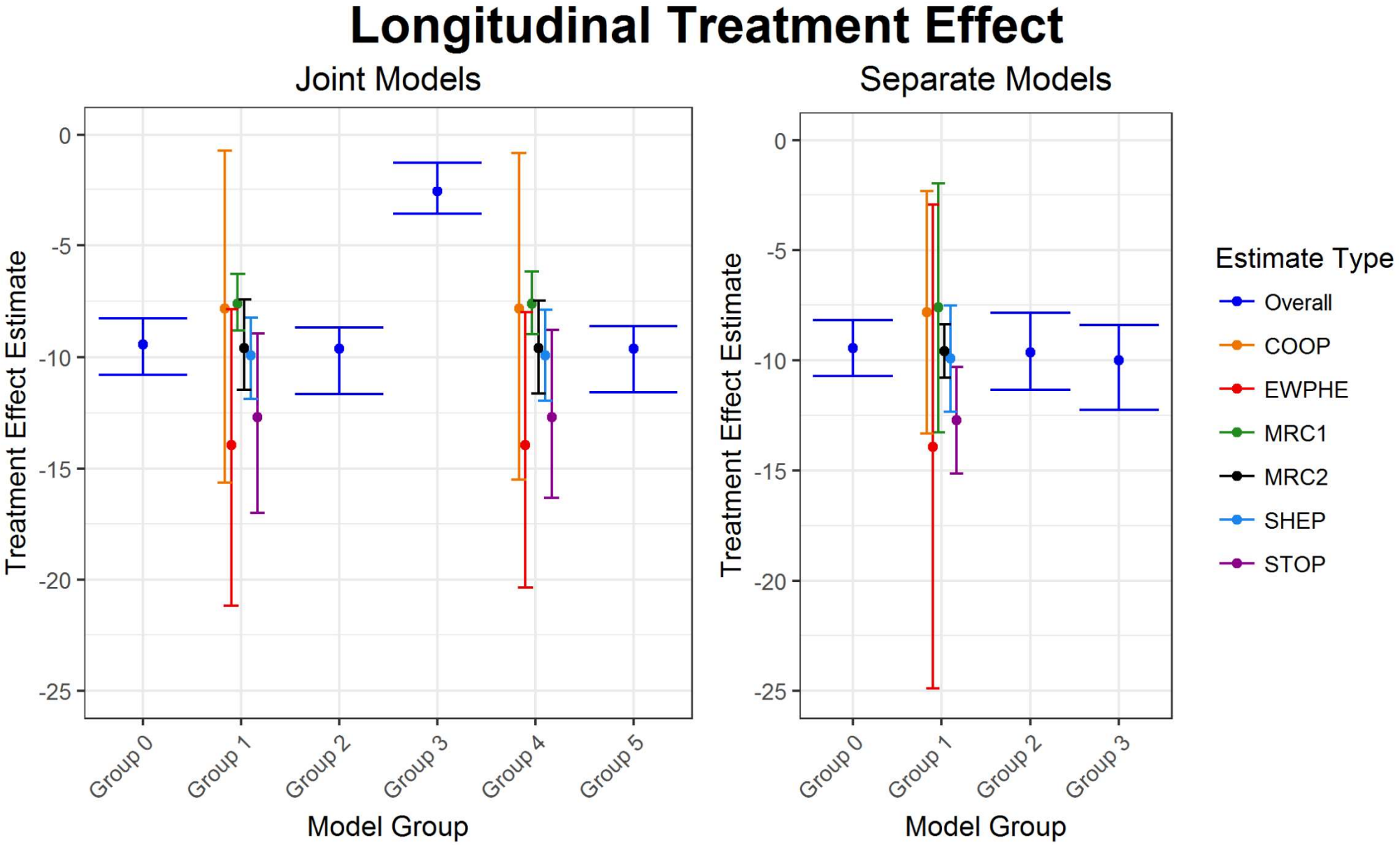
ne stage methods – Group 5 – Fixed effects, stratified baseline zard, one study level random effect

$$Y_{ki} = \beta_{10} + \beta_{11} time_{ki} + \beta_{12} \exp(-3 * time_{ki}) + \beta_{13} treat_{ki} + \beta_{14} study_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} + b_{1k}^{(3)} treat_{ki} + \varepsilon_{ki}$$

$$\lambda_{ki}(t) = \lambda_{0k}(t) \exp(\beta_{21} treat_{ki} + W_2)$$

$$W_2 = \alpha^{(2)} \left(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{ki} \right) + \alpha^{(3)} (b_{1k}^{(3)} treat_{ki})$$

ne stage methods – real data



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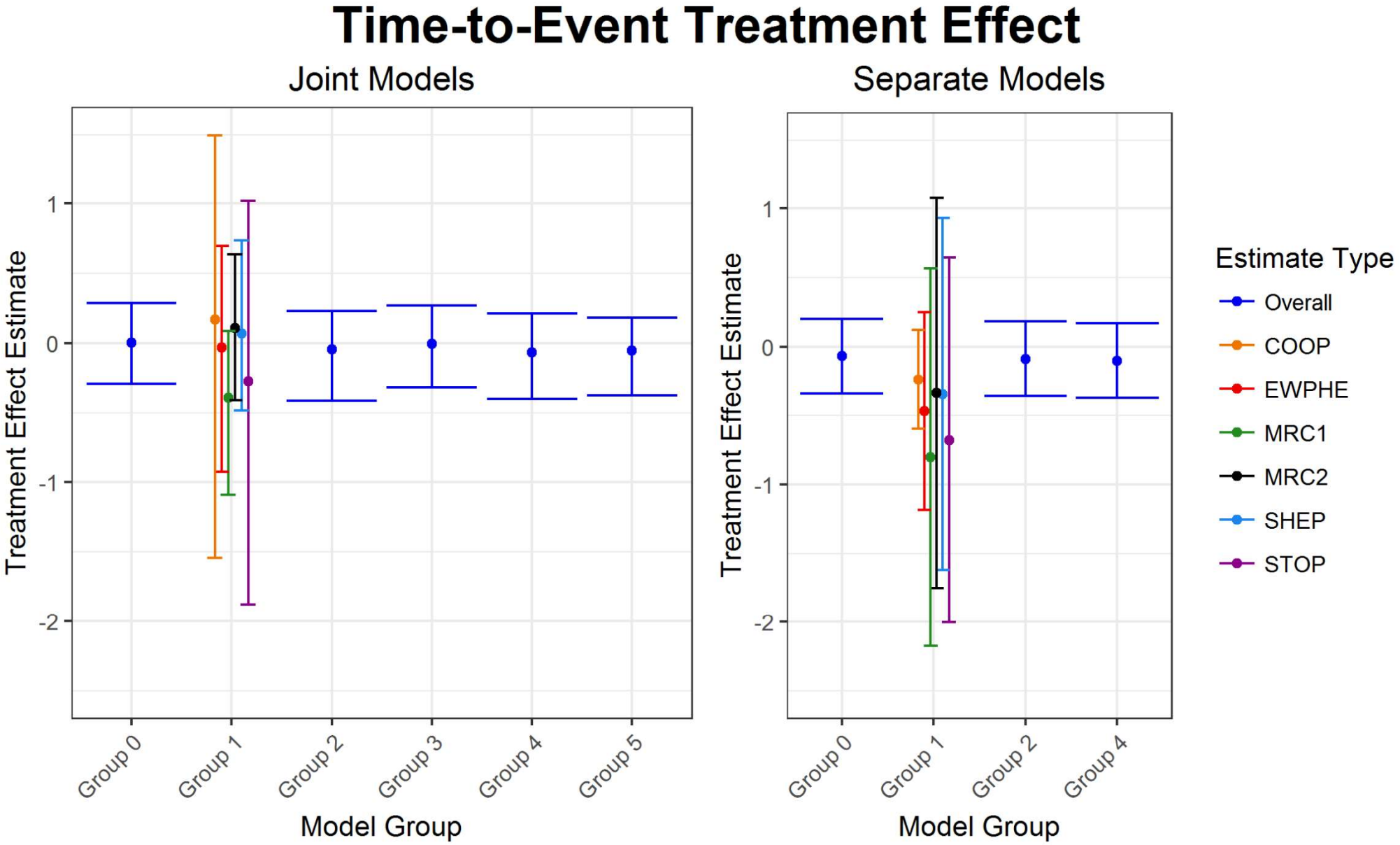

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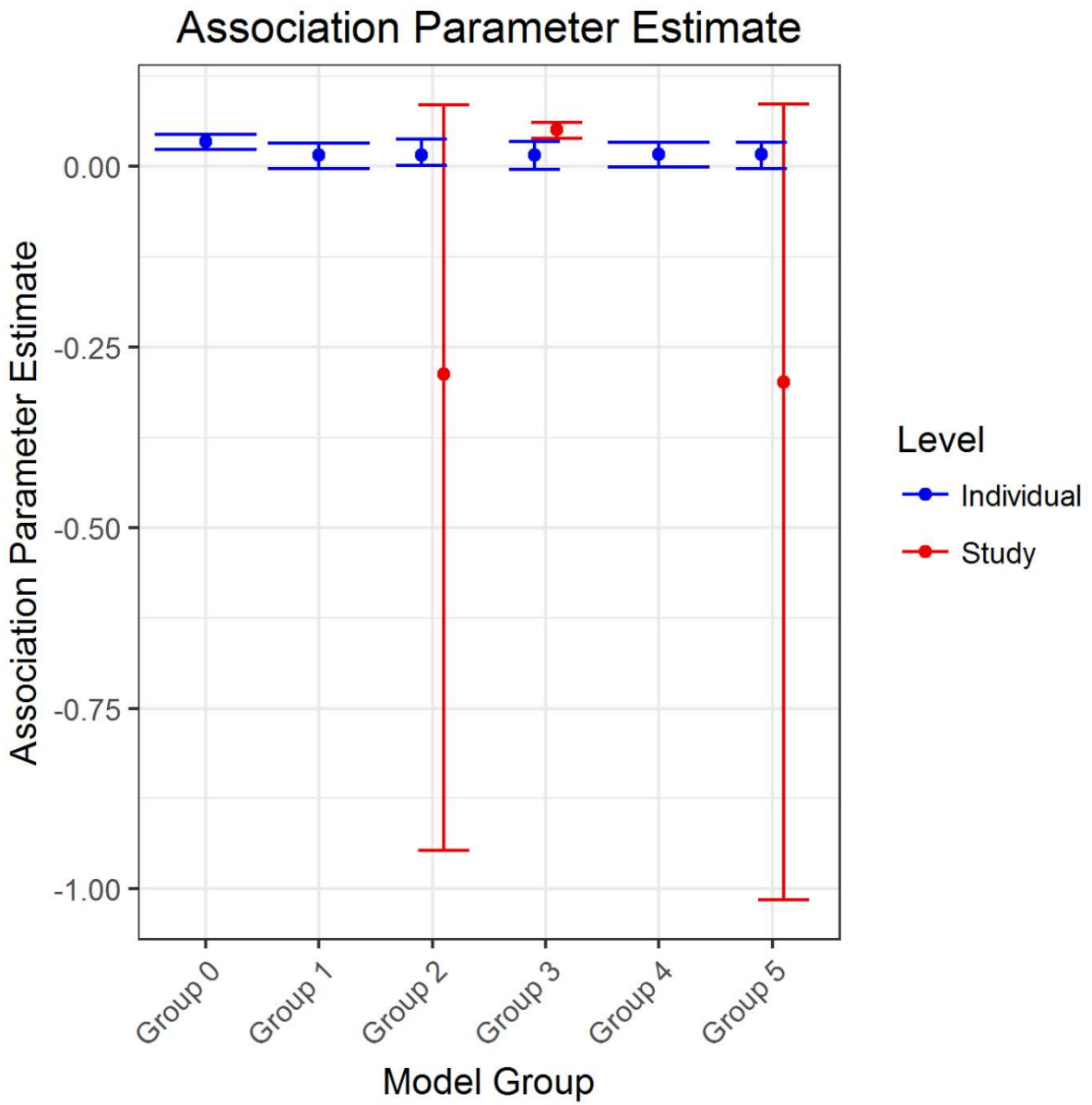

neRmeta

ackage developed as extension to joineR package

Currently one stage model permits

- Random effects only proportional sharing structure
- One continuous longitudinal outcome and one possibly censored time-to-event outcome
- Individual and study level random effects permitted, capped at 3 per level
- Baseline hazard can be common across studies or stratified by study

ackage also contains (but not demonstrated here) :

- Functions to easily plot multi-study joint data
- Multi-study joint data simulation function
- Function for second stage of two stage MA to pool joint model fits

onclusions

- Care must be taken during two stage meta-analyses of joint data to pool only parameters with comparable interpretations
- A variety of methods exist to model multi-study joint data in a one stage analyses, however some may not be appropriate unless the number of studies in the meta-analysis is over a given threshold
- Functions for analysis of multi-study joint data available in R package joineRmeta

uture Work

- Alternative ways to fit joint model (e.g. EM with Monte Carlo step) to speed up model fitting
- Expansion of permitted association structures

Thank you for listening.
Any questions?